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(54) **Water-soluble derivatives of non-steroidal anti-inflammatory agents and a process for the production thereof**

(57) Pharmaceutical compositions comprise derivatives of non-steroidal acidic anti-inflammatory agents of which the structure comprises an aromatic nucleus having one or more hydrophobic side-chain(s) and an acidic carboxylic group, and a hydrophylic component selected from tris (hydroxymethyl) aminomethane; [bis (2 hydroxyethyl) - amino] - tris (hydroxymethyl) methane, 1,3 - bis [tris (hydroxymethyl) - methylaminopropane, 3 - [tris - (hydroxymethyl) methyl] - aminopropanesulfonic acid, 2 - [tris (hydroxymethyl)methyl] - aminoethanesulfonic acid and N - [tris (hydroxymethyl) methyl] - glycine or a mixture thereof.

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SPECIFICATION

Water-soluble derivatives of non-steroidal anti-inflammatory agents and a process for the production thereof

The invention relates to watersoluble derivatives of non-steroidal anti-inflammatory drugs and also to therapeutic compositions containing these derivatives.

Non-steroidal anti-inflammatory agents are increasingly used in clinical practice to cure degenerative joint diseases or arthritis and they are used for the treatment of inflammatory locomotor diseases, gout, spondilitis and related diseases. The therapeutic agents are classified in the literature according their chemical character. The common chemical feature of the therapeutic agents used in this invention is an aromatic nucleus with a hydrophobic side-chain (or side-chains) and an acidic group (a carboxylic group). The compounds are hydrophobic (lipophilic) water-insoluble. The oldest representatives of non-steroidal anti-inflammatory drugs are the selicylic acid derivatives, the newer ones are the following:

anthranilic acid derivatives,
indol derivatives,
naphthalene derivatives,
other arylcarboxylic acid derivatives.

The parent compounds are insoluble in water, some of the derivaties rapidly decompose in alkaline solutions; so injectable solutions or other aqueous compositions are not used for therapeutic purposes. Oral administration in the form of tablets, capsules, syrups are usually employed or possibly suppositories are used for the therapy of different diseases in internal medicine, rheumatology, dermatology, stomatology, ophthalmology, surgery, gynacology etc. The wide-spread use in therapy made necessary the production of intestinosolvent drugs. On the other hand, efforts were made to produce water-soluble derivatives of the hydrophobic compounds to enhance absorption, to reduce the effective dose and thus the side-effects.

Indomethacin, well-known since 1963, has been used in clinical practice since 1965 for its efficient analgesic anti-inflammatory and antipyretic properties. Since indomethacin exhibits several undesirable side-effects after oral administration, the search for new therapeutic anti-inflammatory drugs has been continued. Anti-inflammatory agents devoid of nitrogen cause less severe side-effects, but their synthesis per se has not solved the occurrence of potentially very grave adverse effects.

It is well-known that part of the adverse effects of the parent compounds cannot be separated from their therapeutic effect. The anti-inflammatory drugs inhibit enzymes participating in the metabolism of intact tissues also in vitro [Vane, J. R.: Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. Nature New Biology *231*, 232, 1971]. The best-known and most often occurring side-effect is the erosion of the gastric mucosa, which is enhanced by the oral administration of the anti-inflammatory drug. Synthesis of prostaglandin causing inflammation decreases and the mucosa becomes more vulnerable.

Several investigations were performed for the application of anti-inflammatory drugs in an aqueous medium (to produce suspensions and solutions) by means of combining anti-inflammatory agents with different compounds, therapeutic vehicles or surface-active-agents. To increase dissolution of indomethacin, flufenamic acid or metenamic acid Dambis-Khahl suggested adding urea and 4 - dimethyl - amino - 2,3 - dimethyl - 1 - phenyl - pirrazolidon - 5 - on [Can. J. Pharm. Sci. *11*, 114-117, 1976]. Krusko, E. [Farmaco Ed. Pract. *31*, 463-472, 1976] suggested using non-ionic polyoxyethylene type surface-active agents for the dissolution of indomethacin. Ford, Rubinstein et al. [Pharm. Acta Helv. *53*, 93-98, 1978] studied the interaction of indomethacin and polyethylene glycol (6000). A suspension can be prepared by mixing of 85 per cent of polyethylene glycol and 15 per cent of indomethacin. El Sabbagh, Chanem et al. [Pharmazie *33*, 529,531, 1978] studied the interaction of non-ionic (Tween type) surface-active compounds, indomethacin and urea to increase water solubility of the therapeutic agent. Sanghavi and Kalib [Ind. J. Pharm. Sci. *40*, 239, 1978] use pentaerythritol for the aqueous suspension of indomethacin. Pawolczyk, E., Knitter, B. [Kinetics of drug degradation. Part 58: Method of preparation and stability of 3% aqueous indomethacin solution. Pharmazie *33*, 586-588, 1978] produced a stable aqueous solution containing 3 per cent of indomethacin, by means of boiling the therapeutic agent with ethylurea and ethylcarbamate. The so-obtained diluted solutions, however, have not come into general use. Hamada et al. [Chem. Pharm. Bull. *23*, 1205-11, 1975] made efforts to increase the dissolution of flufenamic acid and mefenamic acid using different auxiliary agents.

In spite of the great number of experiments there is no suitable method known for the intravenous, intramuscular, local, intra-articular, subconjunctival administration or for the distillation of eye-drops of non-steroidal acidic anti-inflammatory agents. The amount of dose and the degree of side-effects thereof could not be changed therefore to date.

An aim of the invention is the production of water-soluble derivatives of non-steroidal acidic anti-inflammatory agents suitable for therapeutic use, especially for peritoneal or other injection and suitable for local application, whereby the therapeutic range of these agents may be increased, and the amount of dose may be decreased, while maintaining the efficacy of these agents. The administration of these agents should be allowed even in those cases where the basic compounds could not be used due to undesirable side-effects. The application of these agents should also be possible in those acute cases where a greater amount of dose assures a rapid therapeutic efficacy and recovery of the patient.

According to the invention non-steroidal acidic anti-inflammatory agents comprise compounds which have an aromatic nucleus with one or more hydrophobic side-chains and an acidic (carboxylic) group and can be classified according the following:

(a) salicyclic acid derivatives:
aspirin (acetylsalicylic acid);
(b) anthranilic acid derivatives:
flufenamic acid 2 - [3 - (trifluoromethyl) anilino] - benzoic acid
niflumic acid 2 - [3 - (trifluoromethyl) anilino] nicotinic acid
mefenamic acid N - (2,3 - xylyl) anthranilic acid
(c) indol derivatives:
indomethacin 1 - (p - chlorobenzoyl) - 5 - methoxy - 2 - methylindole - 3 - acetic acid;
(d) naphthalene derivatives:
naproxen d - 2 - (6 - methoxy - 2 - naphthyl) propionic acid;
(e) other arylcarboxylic acids:
aclofenac 4 - allyloxy - 3 - chlorophenylacetic acid;
fenoprofen α - dl - 2 - (3 - phenoxyphenyl) propionic acid;
ibuprofen (2 - (4 - isobutylphenyl) propionic acid);
ketoprofen (2 - (3 - benzoylphenyl) propionic acid);
phenbuphen ((3,4 - biphenyl) carbonyl propionic acid);
metizianic acid (10 - methyl - 2 - phenothiazinyl acetic acid).

To prepare the watersoluble derivatives of the anti-inflammatory agents the following hydrophilic compounds are used:

[tris(hydroxymethyl)aminomethane] (TRIS)
[bis(2-hydroxyethyl)-amino]tris(hydroxymethyl)methane] (BIS-TRIS)
{1,3-[tris(hydroxymethyl)methylamino]-propane} (BIS-TRIS-PROPANE)
3-{[tris(hydroxymethyl)methyl]amino}-propane-sulfonic acid (TAPS)
2-{[tris(hydroxymethyl)methyl]amino}-ethane-sulfonic acid (TES)
N-[tris(hydroxymethyl)methyl]glycine (TRICINE)

According to the invention the water-soluble derivatives of the anti-inflammatory agents contain at least one mol of the hydrophilic compound per mol anti-inflammatory drug; in general the latter can be used also in surplus amount.

The water-soluble derivatives of the acidic anti-inflammatory agents are produced by means of contacting the anti-inflammatory agent with the hydrophylic component or its solution which can be aqueous or a solution in a suitable organic solvent. Expediently the hydrophilic compound is dissolved in water or in a polar organic solvent and thereafter the anti-inflammatory agent is added. The new derivative can be separated, if necessary, by evaporating the solvent or the water in vacuo. The thus obtained residue forms the compound to be used for therapeutic purposes.

The invention comprises therapeutic compositions, and the production thereof, which contain an above-mentioned non-steroidal acidic anti-inflammatory agent and a hydrophylic compound in a suitable molar ratio with adjuvants and/or ingredients.

For the purpose of local treatment the solutions of the non-steroidal acidic anti-inflammatory agents are incorporated into eye-drops or ointments. In these compositions generally therapeutically active compounds compatible with the therapeutic agents of the invention can be used as well.

The therapeutic compositions can be employed as anti-inflammatory, antipyretic and analgesic drugs. They inhibit prostaglandin synthetase activity *in vitro*. The concentrations of the aqueous solutions of the above mentioned drugs are 10-100 mg./ml. or above, pH values of the solutions are about 6.8-8.5. The compounds produced according to the invention can be stored in the form of a powder for years.

The derivatives according to the invention can be applied intravenously, intramuscularly, intraarticularly, subconjunctivally or in the form of eye-drops. It is highly advantageous that the instant derivatives are readily soluble in water and lipids as well; e.g. the partition coefficient (K) of the derivative according to the invention of indomethacin in chloroform/water is 1.0. This favourable partition coefficient ensures diffusion of the therapeutically active compound through the cell membrane and ensures thereby constant high tissue level. Derivatives prepared according to the invention are bound, presumably, in the blood vessels to serum albumin similar to the parent compounds and they exert no tissue-damaging effect. The derivatives prepared according to the invention and administered intravenously proved to be 4 times more effective in the carrageen induced edema test than the parent compound after oral administration.

The application of the present invention to different non-steroidal anti-inflammatory drugs and routes of administration are exemplified in but not limited to the following Examples.

Example 1

Composition for therapeutic use is prepared from the following compounds:

Dry fill	25 mg. indomethacin
Dissolving ampoule	50 mg. TRIS in 2 ml. distilled water.

After having dissolved the dry fill in the solvent, the final pH is 6.8. The so-obtained solution inhibits prostaglandin synthetase activity in 90 per cent.

The therapeutic agent, being non-irritant, can be applied intravenously, intramuscularly, intraarticularly, subconjunctivally or as eye-drops.

Sterile purulence in the aqueous humour, a consequence of increased permeability, is diminished by instillation of eye-drops or subconjunctival injection. Injection of arachidonic acid into one eye of a rabbit increased protein content of the aqueous humour 10-fold in consequence of the increased permeability. After pretreatment of the other eye with indomethacin eye drops the normal protein content of the aqueous humour prescribed.

Example 2

For the isolation of water-soluble indomethacin derivative 1000 g. of indomethacin are dissolved in 10 litres of methanol with constant stirring at room temperature and thereafter 1000 g. TRIS in 1 litre of methanol are added. The thus obtained solution is slightly heated and evaporated *in vacuo*. Care must be taken not to exceed 20°C. The obtained white crystalline compound can easily be dissolved in

water. In a concentration of 100 mg./ml. the pH is 6.4. The melting point of the compound is 148°C after recrystallization from acetone-ethylether.

The therapeutic composition can be used according Example 1. It can be used also in a mixture with suitable ingredients orally when filled in capsules.

Example 3

For ophthalmological purposes 50 mg. of indomethancin,36 mg. of TRIS, 10 mg. of citric acid and 10 mg. of boric acid are mixed and the dry mixture is filled into capsules. The content of the capsules can be dissolved in 10 ml. of water. The pH of the thus obtained solution is 7.3 and the solution is isotonic. The solutions can be used as eye-drops.

Example 4

Ointment for local treatment is made up by preparing 1 ml. solution of the indomethacin derivative according Example 1, and by mixing the so obtained aqueous solution with 0.045 g. of cholesterol, 0.090 g. of paraffin oil and 2.895 g. of yellow liquid paraffin. The indomethacin ointment has a local anti-inflammatory activity and can be used as a sun-cream.

Example 5

The indomethacin solution prepared according to Example 1 is lyophilized. After dissolving the dry residue in 1 ml. of water, the obtained solution can be used for similar therapeutic purposes as mentioned in Example 1.

Example 6

A pharmaceutical composition is prepared from the following components:

Dry fill	50 mg. indomethacin
Dissolving ampoule	80 mg. N-[tris(hydroxy-methyl)-ethyl] glycine (TRICINE)
	2 ml. distilled water

Administration: as in Example 1.

Example 7

A pharmaceutical composition is prepared from the following components:

Dry fill	50 mg. indomethacin
Dissolving ampoule	70 mg. 1,3-bis[tris hydroxymethyl)-methylamino]-propane-sulfonic acid
	10 mg. sodium pyrosulfite
	30 mg. polyvinyl pyrrolidone
	2 ml. distilled water

Administration: same as in Example 1.

Example 8

A therapeutic composition is prepared from the following components:

Dry fill	50 mg. indomethacin
Dissolving ampoule	120 mg. 3-[tris(hydroxy-methyl)-methylamino] ethanesulfonic acid
	2 mg. sodium pyrosulfite
	20 mg. polyvinyl alcohol
	2 ml. distilled water

Administration: as in Example 1.

Example 9

A pharmaceutical composition is prepared from the following components:

Dry fill	230 mg. naproxen d-2-(6'-methoxy-2'-naphthyl)-propionic acid
Dissolving ampoule	360 mg. TRIS
	10 ml. distilled water

After having dissolved the dry fill in the solvent, the final pH = 8.0. Administration: as in Example 1.

Example 10

Water-soluble naproxen is isolated by dissolving 230 mg. of naproxen in 5 ml. of methanol and 180 mg. of TRIS and by subsequent evaporating the solvent at 25°C. When the dry residue is dissolved in 10 ml. of water, the pH is 8.0. The clear solution can be stored for 1 week at 4°C. without reduction of the therapeutic efficacy.

Example 11

For the production of watersoluble niflumic acid 2800 mg. of niflumic acid (2 -[3 - trifluoromethyl) anilino] - nicotinic acid) are dissolved in 500 ml. of methanol, and 3600 mg. of TRIS in 400 ml. of methanol are added. After complete dissolution the solution is filled up to 1000 ml. 50-50 ml. samples are evaporated in vacuo. The dry residues are equivalent to 140 mg. niflumic acid each. The dry residue can be stored at room temperature for years without reduction of efficacy.

The dry residue can be dissolved in 2.5 ml. of distilled water and can be administered parenterally. The aqueous solution can be stored at 4°C for 1 week without reduction of efficacy.

Example 12

A pharmaceutical composition is prepared from the following components:

Dry fill	50 mg. fenoprofen (α-dl-2-(3-phenoxy-phenyl)propinic acid)
	72 mg. ethylenediamine-tetra-acetic acid
Dissolving ampoule	144 mg. TRIS
	2 ml. distilled water

After having dissolved the dry fill in the solvent, the pH is 7.2. Administration: as in Example 1.

Example 13

A pharmaceutical composition is prepared from the following components:

Dry fill	230 mg. naproxen [d-2-(6'-methoxy-2'-naphthyl)-propionic acid]
Dissolving ampoule	430 mg. BIS-TRIS-PROPAN
	10 ml. distilled water

After having dissolved the dry fill in the solvent, the pH is 7.9. Administration: as in Example 1.

Example 14

A pharmaceutical composition is prepared from the following compounds:

Dry fill	200 mg. acetylsalycilic acid
Dissolving ampoule	790 mg. TRIS
	10 ml. distilled water

After having dissolved the dry fill in the solvent, the final pH is 7.8. The solution can be administered as in Example 1. The dry fill can be filled in capsules

and administered orally.

CLAIMS

1. Derivatives of non-steroidal acidic anti-inflammatory agents, the anti-inflammatory molecule of which comprises an aromatic nucleus, containing one or more hydrophobic side-chain(s) and an acidic carboxylic group, and a hydrophylic component selected from tris (hydroxymethyl) aminomethane; [bis)2 - hydroxyethyl) - amino] - tris (hydroxymethyl) methane, 1,3 - bis[tris (hydroxymethyl) - methylaminopropane. 3 - [tris - (hydroxymethyl) methyl] - aminopropanesulfonic acid, 2 - [tris (hydroxymethyl) methyl] - aminoethanesulonfic acid and N - [tris (hydroxymethyl) methyl] glycine or a mixture thereof.

2. Derivatives according to claim 1 comprising acetylsalicylic acid as anti-inflammatory agent, and a hydrophilic component.

3. Derivatives according to claim 1 comprising flufenamic acid [2 - (3 - trifluoromethylanilinobenzoic acid] and a hydrophilic component.

4. Derivatives according to claim 1 comprising niflumic acid (2 - [3 - trifluoromethyl) anilinol-nicotinic acid) and a hydrophilic component.

5. Derivatives according to claim 1 comprising mefenamic acid (N - 2,3 - xylyl) anthranilic acid) and a hydrophilic component.

6. Derivatives according to claim 1 comprising indomethacin (1 - (p - chlorobenzoyl) - 5 - methoxy - 2 - methylindole - 3 - acetic acid) and a hydrophylic component.

7. Derivatives according to claim 1 comprising naproxen (d - 2 - (6 - methoxy - 2 - naphthyl) propionic acid) and a hydrophylic component.

8. Derivatives according to claim 1 comprising aclofenac (4 - allyloxy - 3 - chlorophenylacetic acid) and a hydrophylic component.

9. Derivatives according to claim 1 comprising fenoprofen (α - dl - 2 - (3 - phenoxyphenyl) propionic acid) and a hydrophylic component.

10. Derivatives according to claim 1 comprising ibuprofen (2 - (4 - isobutylphenyl) propionic acid) and a hydrophylic component.

11. Derivatives according to claim 1 comprising ketoprofen (2 - (3 - benzoylphenyl) propionic acid) and a hydrophylic component.

12. Derivatives according to claim 1 comprising phenbuphen ((3,4 - biphenyl) carbonyl propionic acid) and a hydrophylic component.

13. Derivatives according to claim 1 comprising metizianic acid (10 - methyl - 2 - phenothiazinyl acetic acid and a hydrophylic component.

14. Derivatives according to any one of the preceding claims comprising at least 1 mol hydrophylic component per mol anti-inflammatory agent.

15. A process for preparing derivatives of acidic non-steroidal anti-inflammatory agents which comprises contacting one mol of a non-steroidal acidic anti-inflammatory agent and at least 1 mol of a hydrophilic component in an aqueous or a polar organic solvent and, if desired, isolating the product after removing the solvent.

16. A process according to claim 15 where the hydrophilic component is dissolved in water or another solvent and the non-steroidal anti-inflammatory compound is added as a solid substance.

17. A process according to claim 15 or claim 16 wherein the derivative is obtained by evaporating the water or the solvent used, preferably below 30°C.

18. A process as claimed in claim 15 substantially as hereinbefore described in any one of the Examples.

19. A derivative when produced by a process as claimed in any one of claims 15 to 18.

20. A derivative as claimed in claim 1 substantially as hereinbefore described in any one of the Examples.

21. Pharmaceutical compositions especially for analgesic, anti-inflammatory, anti-phlogistic and anti-pyretic purposes in the form of parenteral injections or eye-drops comprising the derivatives according to any one of claims 1 to 14 and 18 to 20 and an adjuvant, or an ingredient used in pharmaceutical compositions.

22. The therapeutic application of the new derivatives according to any one of claims 1 to 14 and 18 to 20 for pharmaceutical, especially analgesic, anti-inflammatory, antiphlogistic and antipyretic purposes.

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